



AMERICAN VETERINARY MEDICAL ASSOCIATION

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Dockets Management Branch (HFA-305)
Food and Drug Administration
Park Building, Rm. 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Docket No. 97N-0217 -- Minor Use/Minor Species
Discussion Draft

Dear Food and Drug Administration:

The American Veterinary Medical Association is pleased to respond to the Discussion Draft addressing Proposals to Increase the Availability of Approved Animal Drugs for Minor Species and Minor Uses. We appreciate the FDA-CVM's efforts to solicit comments from interested parties and applied this cooperative spirit. The Center is to be commended for the incorporation of concepts which depart greatly from the current situation into the Discussion Draft. The range of ideas presented, clarity in requirements, and attention to detail show a conscientious effort on the part of the Center to consider some large scale changes which have the potential to increase the number of drugs available for minor uses.

The following AVMA comments address, in sequential order, the proposals found in the Discussion Draft

PROPOSALS TO INCREASE THE NUMBER OF APPROVED ANIMAL DRUGS FOR MINOR USE

A. MODIFICATION OF EXTRALABEL PROVISIONS

LEGISLATIVE ACTION:

Amend the FD&C Act to modify the prohibition on extralabel use of medicated feeds to allow such use in minor species.

REGULATORY ACTION:

Amend the corresponding regulations to accommodate this change.

CVM FUNCTIONAL CHANGES:

None.

PARTICULAR ISSUES ON WHICH FDA SEEKS COMMENT

Q. Will the proposed modification of extralabel provisions and suggested sunset period provide adequate and appropriate temporary relief until approved products are made available, or will it serve as a disincentive to the pursuit of approvals?

Comments:

The AVMA is pleased that the AMDUCA provided veterinarians with the legal authority to use drugs in an extralabel manner, when needed, and in compliance with the regulations. But the Association recognizes that the AMDUCA unintentionally had the consequence of effectively excluding some minor species industries from access to legal extralabel drug use, namely those which rely on drugs administered through medicated feeds. To remedy this situation, the AVMA urges the FDA to implement the concept proposed by the Minor Species Animal Health Coalition, of which AVMA is a member. Under this concept, the Veterinary Feed Directive (VFD) is used as the vehicle for providing medicated feeds to minor species, rather than the prescription which is reserved for extralabel use of dosage form drugs under AMDUCA. The benefits of this approach are that a veterinarian directs the use of medicated feed for minor species, the process is documented by the VFD form requirements, and the current feed distribution system is not disrupted. The AVMA urges that this concept be implemented whether as a matter of enforcement discretion, or as an amendment to Section 504 of the FD&C Act. AVMA is in general agreement with the January 19, 1998 comment of the Coalition on Animal Health on this matter.

This provision is not a substitute for drug approval. A sunset clause would be appropriate to allow a sponsor to fulfill the requirements of a supplemental NADA. The aquaculture, gamebird and other industries are in dire need of drugs today, and sales dollars obtained through minor species use could be used by the sponsor toward funding necessary studies. The AVMA does not believe this VFD concept would discourage the long term goal of formal approval, particularly when incentive and/or exclusivity programs are offered to sponsors and producers. Gamebird and aquaculture industry members currently participate in field studies, and these industries recognize the long term need for these drugs.

Q. Should the proposed modifications be extended to include reproductive hormones and implants?

Comments:

It is the opinion of the AVMA that the extralabel use of reproductive hormones should be included under AMDUCA -- both for minor species and minor usage in major species. The same is true for implants used to control reproductive cycles. However, implants that are growth and production in purpose should be excluded.

B. REMOVAL OF DISINCENTIVES

1. **Lack of Enforcement Resources**
2. **Changes in the Standard for Regulatory Action**
3. **Assurance that an Existing Approval Would Not be at Risk**

CONGRESSIONAL ACTION:

1. A line-item budgetary change to increase resources for CVM minor use enforcement.
2. Amend the FD&C Act to permit the removal of a minor use animal drug from the market on the sole basis that it lacks FDA approval for the purposes for which it is labeled or promoted.

FDA ACTION:

Amend 21 CFR 514.106 to define supplemental NADAs for the addition of minor species to major species labels as a category that would not trigger critical reviews of the original major species data packages.

CVM ACTION:

Designate a Minor Use Advocate within the Office of Surveillance and Compliance and ensure that minor use actions are included in CVM's overall enforcement strategy.

Comments:

The existence of unapproved drugs in the marketplace may be a deterrent to a drug sponsor contemplating a minor use approval for the same or similar drug. However, those unapproved drugs (many for which the agency practices enforcement discretion) may be filling a critical need. Henceforth, efforts to expedite the removal of these drugs may be detrimental to the animal industries. The AVMA would support prompt removal of an unapproved drug from the market when an approved drug is available.

The third topic related to removing disincentives involves amending the regulations so that sponsors are assured their parent application will not be jeopardized when supplemental NADAs are filed. The Association believes this assurance is vital to the co-operation of sponsors and asks that the 21 CFR amendment be a priority. The AVMA also recommends that this same assurance be extended to sponsors involved in the proposed conditional approval process (part 6) and expert review process (part H).

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- Q. Will the suggested strategies be sufficient to remove the existing direct regulatory disincentives?*
- Q. Are there additional disincentives to gaining approvals that should be removed? How might this be accomplished?*

Comments:

The discussion draft asks if the above three suggested strategies will be sufficient to remove the existing direct regulatory disincentives, or if there are additional disincentives that should be removed. The AVMA feels the animal drug industry is in the best position to make that assessment.

C. ENHANCEMENT OF EXISTING PROGRAMS FOR DATA DEVELOPMENT**1. Expand Established Congressional Research Funds****CONGRESSIONAL ACTION:**

Increase appropriations for the budgets of NRSP-7, Saltonstall-Kennedy Grant Program, Hatch Fund, and National Coastal Research Institute and earmark the funds for minor research.

FDA ACTION:

None.

USDA ACTION:

Expand the scope of the NRSP-7 program to allow the funding of research for non-therapeutic drugs and drugs for non-food producing animals.

2. Establish New Programs Based on the NRSP-7 Model**CONGRESSIONAL ACTION:**

Appropriate funds for the research program.

FDA/CVM ACTION:

None.

3. Establish a Minor Use Database**CONGRESSIONAL ACTION:**

None

FDA/CVM ACTION:

Establish and maintain the minor use database.

Comments:

In keeping with the mission of the USDA, the NRSP-7 program has been confined to food- and fiber-producing animals raised for commercial purposes. However, if additional outside funds were appropriated, we would anticipate the USDA would not object to incorporating non-food species into the NRSP-7 program. The AVMA favors the inclusion of non-food species in the program. Similarly, the scope of program should be broadened to include production drugs.

The Association would be in favor of increasing appropriations for the budgets of the Saltonstall-Kennedy Grants Program, Hatch fund, and National Coastal Research Institute -- and earmarking the funds for minor use research. Such appropriations could enhance aquaculture, production drug, and coastal research primarily.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

Q. Are there additional existing congressional research funds which could be expanded for minor use research?

Comments:

Unknown at this time

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

Q. Would the proposed model program provide a useful supplement to the existing NRSP-7 program?

Comments:

The AVMA favors a research support program administered by a minor use coordinator who would organize research activities for various minor species. The National Aquaculture NADA Coordinator is a good model. We note that the diversity of minor species suggests that a number of coordinators might be necessary, each with species expertise. These individuals should be funded by various public and private institutions.

In regard to the third proposal, we would support the establishment of a Minor use database to assist parties interested in furthering the approval process. It may be, however, that these same parties are already quite familiar with this information.

D. INCENTIVES TO PURSUE MINOR USE DRUG APPROVALS

1. Financial Incentives

- a. Exclusivity for New Claims**
- b. Tax Credits**

2. Negotiation of a Shorter Time frame for the Review of a Major Product

3. Consider Residue Depletion Studies as "Significant New Data" for Exclusivity

CONGRESSIONAL ACTION:

- 1. Amend the FD&C Act to increase protection against generic approval from three years to seven years for NADA supplements for new minor use claims and from five to ten years for new NADAs.**

2. Amend the Internal Revenue Code to allow tax credits to the sponsors of minor use research and to producers who participate in field trials.

FDA/CVM ACTION:

1. Revise policies relating to NADA review priorities to allow for shorter review times for major use NADAs of sponsors of minor use NADAs.
2. Revise policy relating to food safety data to permit residue depletion data to qualify as "significant new data" when appropriate.

Comments:

The Association agrees that the lack of incentive for sponsors to enter the minor use market means that potential generic competition may not be great. However, as other incentives are incorporated, the minor use market may become more interesting to sponsors. The FDA-CVM indicates that extension of protection against generic approval is part of a successful orphan (human) drug program. As such, the AVMA believes the FD&C Act should be amended to increase the period of protection against generic approval from three years to seven years for approval of a supplemental NADA and from five to ten years for an original minor use NADA.

In keeping with the successful human orphan drug program, tax credits should be granted to sponsors of minor use drugs. Given the lower profit margin on animal drugs as compared to human drugs, a 100% tax credit in the year of the expenditure seems quite appropriate. Providing tax credits to minor species producers who participate in clinical field trials also has great merit. Such a proposal has the potential to maximize the collection of field data.

If shortened review times for major use drugs would motivate drug sponsors to include minor uses in the approval, the AVMA would support this action. We would caution, however, that in these days of increasing responsibility and limited resources, the Center may have difficulty fulfilling a commitment to shorter review time frames.

The AVMA favors considering residue depletion studies as "significant new data" for exclusivity, particularly if such a categorization would serve as an incentive for the drug sponsor to conduct such studies. The benefit of freeing up producer groups and NRSP-7 programs to conduct other research seems appreciable. However, if exclusivity were already lengthened, as mentioned above, would a sponsor find residue depletion studies to be a source of incentive, even if they were considered "significant new data" for exclusivity?

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- Q. Is the benefit of extended exclusivity, with respect to fostering initial approval, more important than the risk of increased drug costs that could be associated with*

decreased competition from generic approvals?

Comments:

Ultimately the market will decide if the increased costs associated with exclusivity are bearable. Individual industries might have very different price tolerances.

Q. Would it be a more significant incentive to provide for an extended period of exclusivity for all the claims of the product?

Comments:

The Center asks if it would be a more significant incentive to provide for an extended period of exclusivity for all the claims of the product. It seems likely it would. The AVMA suggests that one year of exclusivity for all label claims might be offered for each minor species supplement. In cases where the major drug is no longer under patent protection exclusivity, perhaps FDA could allow the sponsor to receive an additional year of exclusivity for a product that has not yet completed its period of exclusivity.

**E. DATA SHARING BY MAJOR SPECIES NADA HOLDERS
CONGRESSIONAL ACTION:**

1. Amend the FD&C Act to create a system whereby the Agency can consider data underlying NADAs for minor uses, once the drugs are subject to generic competition or have been abandoned or withdrawn.

FDA/CVM ACTION:

None.

Comments:

If FDA can consider data in underlying NADAs for major uses when the drugs are subject to generic competition or have been abandoned or withdrawn, it seems reasonable that FDA could consider such data when sponsors seek minor use drug development.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

Q. Is it fair to require the sharing of data?

Comments:

A benefit of an imposed data sharing requirement might be the granting of up to one year of exclusivity on another major product.

Q. How could potential liability be ameliorated under such a data sharing system?

Comments:

The animal drug industry is in the best position to answer this question.

F. CREATION BY STATUTE OF A "MINOR USE ANIMAL DRUG" PROGRAM**1. Create a Statutory Category of Minor Use Animal Drugs****CONGRESSIONAL ACTION:**

Amend the FD&C Act to create a category a Minor Use Animal Drugs.

AGENCY/CVM ACTION:

Develop regulations to implement changes in the Act creating Minor Use Drugs.

2. Minor Use Animal Drug Development**CONGRESSIONAL ACTION:**

Amend the Act to create the category of "Minor Use Animal Drugs" and to provide the associated package of incentives.

AGENCY/CVM ACTION:

Create a work unit within CVM to assume responsibility for Minor Use Animal Drug tasks. Promulgate regulations to implement proposed changes to the Act creating "Minor Use Animal Drug" category.

Comments:

The AVMA supports creation by statute of a "Minor Use Animal Drug" program. Such a program would include the statutory category of minor use animal drugs and an FDA-CVM internal work unit to administer the policies associated with such a category. However, the condition that the Agency be given the discretion to designate a new animal drug to be a minor use animal drug based on public health need sounds unnecessarily limiting. Our concern is that production drugs would be excluded, as would drugs containing a second active ingredient to address a disease or condition for which a minor species drug is already approved. In each of these cases the public health concern may not be great and yet the drugs may be important to the animal industry. The AVMA agrees it would be beneficial to construct a minor use animal drug development section within CVM. This unit would determine whether proposed drugs qualify for minor use designation and its resulting incentives. The approach should not be laborious and should instead be minimalist in nature so as to encourage all sorts of minor use drugs. Including minor use application review responsibilities may well free up the office of New Animal Drug Evaluation from new burdens, but these responsibilities can not allow the qualification process for minor use drugs to slow down.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

Q. Are the incentives associated with this strategy a necessary component of the overall proposed "Minor Use Animal Drug Program"?

Comments:

In answer to the question, yes, the incentives associated with this strategy are a necessary component.

G. CONDITIONAL DRUG APPROVAL FOR MINOR USES INVOLVING NON-FOOD ANIMALS

CONGRESSIONAL ACTION:

Amend the FD&C Act to allow conditional approvals of minor use drugs. *(For all animals)*

AGENCY/CVM ACTION:

None.

Comments:

The AVMA believes that conditional drug approval is a reasonable approach to enhancing the number of minor use drugs available and agrees that this system should help companies with limited cash flow to get products to market and offset development costs as the company works toward approval of the product. The AVMA understands the FDA's approach to limitation of this approval method to non-food animals, as tolerance and withdrawal time information should generally be included in a drug which is marketed and promoted for food animal use. But we believe non-food stages of food producing animal life cycles should be included in the conditional approval proposal if there is no practical use for the drug in later life stages. Furthermore, we believe there may be drugs which don't present a residue risk and are needed by minor species food animals. Therefore, the conditional drug approval approach should not automatically exclude food animal drugs.

The AVMA concurs that manufacturing chemistry requirements should be completed prior to obtaining conditional approval, to ensure batch to batch consistency. Without such consistency, reasonable conclusions can not be drawn from field data. A reasonable expectation of target animal safety and effectiveness, and reasonable data for establishing a conditional dose seem appropriate, as does the provision of such information from the literature or a pilot study. Of course the conditionally approved product should be subject to full post-approval reporting requirements. The AVMA concurs with a five year conditional approval period, with annual review for progress toward completion, and revocation in the absence of such progress.

Similarly, at this point in time, most of the Agency's proposed limitations seem

reasonable: that the drug production quantity be established and enforced, that the label indicate conditional status and that if this status were prominently included, promotion would be permitted, and that no second conditional approval would be granted for the same product. The AVMA does not believe products with conditional approvals should be required to have separate labeling and packaging from major species label. The sponsor should be able to add a minor use conditional approval to a major species label as long as the conditional nature of the minor species approval is clearly stated. The AVMA believes the extralabel use of conditionally-approved minor use drugs is acceptable. Such use, when in food animals, would be dependent on the availability of adequate food safety data to determine an adequate withdrawal time as is described under AMDUCA.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

Q. Would the proposed constraints upon conditional approval provide sufficient consumer protection and still provide adequate incentive to pursue a conditional drug approval to final approval?

Comments:

In response to the question regarding the sufficiency of consumer protection, the AVMA would envision that conditionally approved drugs would be available as veterinary prescription drugs only, not OTC drugs. Such an arrangement would incorporate the veterinarian-client-patient relationship and the communication of the conditional nature of the drug approval.

H. ALTERNATE APPROVAL STANDARD/EXPERT REVIEW PANELS FOR MINOR USES INVOLVING NON-FOOD ANIMALS

1. The Expert Review Panel (ERP)
2. Alternate Standard for Approval Under This Model
3. Limitations of Approvals Under This Model

CONGRESSIONAL ACTION:

1. Amend the FD&C Act to create an alternate approval standard for minor use drugs intended for non-food animals.
2. Amend the FD&C Act to allow for the creation and use of expert panels to review minor use drugs intended for non-food animals.

FDA/CVM ACTION:

None.

Comments:

The use of expert review panels (ERP) with an alternate approval standard is a useful approach for minor species drug approvals. Use of a risk based approach whereby the risk to the animal of approving the drug clearly outweighs the risk of not approving the drug is an acceptable standard.

The Agency's description of the ERP charge to review, report, and recommend seems appropriate, including its three member minimum, either as a recognized professional organization or an ad hoc panel. It is acceptable that the ERP would not be totally funded by FDA, but the agency should have some financial obligation since the ERP system would free-up CVM personnel who might otherwise have to be involved. Supplemental funds could be generated by species/breed organizations, producer groups, professional veterinary associations, and drug sponsors.

The CVM addressed alternate standards for approval under this model. In the draft discussion CVM identified that the ERP could accept data other than adequate and well-controlled studies, or studies conducted under Good Laboratory Practices. Also the panel could accept data using a product other than the proposed final market formulation with minimal bridging information, and incorporate generally known information. Additionally, the panel may extrapolate within drug classes in a given species. The AVMA supports use of these alternate standards.

The AVMA believes that the extralabel use provisions of the AMDUCA should be extended to drugs approved under this alternate standard. Again, any extralabel use in food animals would be subject to the existence of adequate food safety data to determine a withdrawal time.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

Q. Will animal caretakers find drugs approved under the proposed alternate standard (with associated restrictions) acceptable?

Comments:

Yes.

Q. Do the affected industries have the needed expertise and/or will they be willing to fund the expert review panels?

Comments:

We believe needed experts exist and that FDA plus industry funding would be adequate.

Q. Is the proposed process appropriately restricted to minor uses involving non-food animals?

Comments:

No, if adequate food safety data are available to the expert review panel and FDA, then minor species food animal uses should not be automatically excluded from the expert review panel proposal.

I. INTERNATIONAL HARMONIZATION

1. Harmonization of the Review Process

CONGRESSIONAL ACTION:

None.

AGENCY/CVM ACTION:

To establish a system to determine that a foreign country's requirements and systems for approving animal drugs are equivalent to the United States' requirements and systems.

2. Identification of Existing Foreign New Animal Drug Approvals and/or Data

CONGRESSIONAL ACTION:

None.

AGENCY/CVM ACTION:

Establish program to identify minor use drugs approved in other countries and work with sponsors to submit data in support of approvals in the United States.

3. Harmonizing Approval Requirements

CONGRESSIONAL ACTION:

None.

AGENCY/CVM ACTION:

Add minor use component to its current harmonization activities.

Comments:

If the U.S. currently accepts importation of food products derived from animals which were treated with foreign approved drugs, it seems reasonable that the foreign approval data would be adequate to gain FDA approval of the drug. Thus, the AVMA believes a system should be established which determines when a foreign country's requirements and systems for approving animals drugs are equivalent to the U.S. requirements and systems. It is acceptable that in order to accept reviews from other countries the drug would need to be intended for use in the same species, and the labeling would bear the same claims unless the sponsor provided data in support of the differences. In addition, the AVMA supports the harmonization of drug approval requirements.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

Q. Could non-governmental input facilitate equivalency determinations?

Comments:

Yes.

Q. Are there sufficient numbers of foreign approvals to justify establishing this program?

Comments:

We suspect so. This information could be confirmed quickly.

Q. Should the proposed differences in approval, standards, processes, and data requirements between major and minor species be included in international harmonization activities?

Comments:

Yes, it is a fact of life that the standard NADA system and lack of economic incentives to sponsors means these alternate mechanisms are necessary, and should be included in harmonization plans.

On behalf of our nearly 63,000 members we are most pleased to contribute our comments on this important issue.

Respectfully,



Bruce W. Little, DVM
Executive Vice President

BWL/ECG/jld